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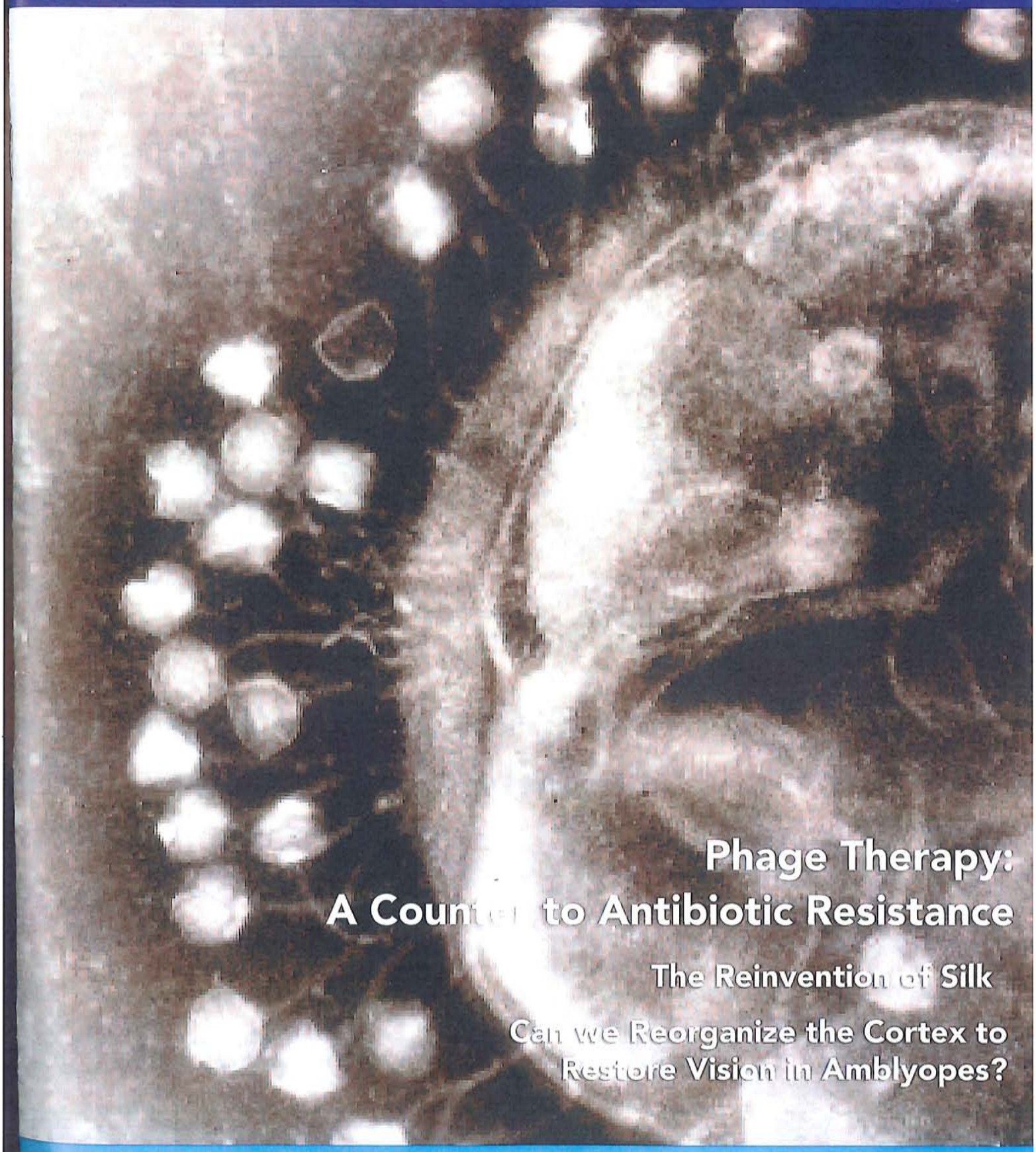

Phage Therapy: A Counter to Antibiotic Resistance

The Reinvention of Silk

Can we Reorganize the Cortex to Restore Vision in Amblyopes?

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Can we reorganize the cortex to restore vision in amblyopes?

Mark Nicholas and Diego Pafundo

Vision is a wonderful process that allows us to interpret our surroundings. Human behavior heavily relies on visual input and thus disorders of the visual system have a strong impact on our lives.

Amblyopia is a major neurodevelopmental disorder which results in the characteristic symptom and common name, "lazy eye". This disorder of the visual system affects approximately 3% percent of the population, and is the most common cause of vision problems in children. Amblyopia develops during childhood as a result of abnormal visual experiences, such as: strabismus or squint, anisometropia (a condition in which the two eyes have unequal refractive power resulting in a blurred retinal image) and monocular deprivation (an opacity that prevents visual input to one of the eyes). As a consequence, amblyopes present persistent deficits in visual cortical processing even when normal input to the visual cortex is restored [1].

> "Firstly, in many cases where children present a mild form of amblyopia, the condition will remain undetected until tested further at older ages when it is too late for successful treatment."

During early childhood, the disease can be produced by a misalignment between the image that each of the two eyes see, triggering a reorganization of the visual cortex. In the case of deprivation, the primary visual cortex does not receive sufficient input from the ablyoptic eye and thus the primary visual cortex reorganizes to prefer the input from the good eye. In the case of strabismus or anisometropia, on the other hand, the child brain can suppress the input of one eye to prevent double vision. Interestingly, persistent alterations in the visual cortex can be produced in early development, whereas altered visual perception in the adult does not induce persistent effects, and conversely, in the case of amblyopes, normal function of the visual system is not recovered once the normal visual perception is restored in the adult state. This phenomenon was studied in the seminal works by the Nobel laureates David H. Hubel and Torsten Wiesel, which described that the visual cortex can be reorganized during a period of increased plasticity, known as the critical period [2-4]. During this critical period, the visual cortex presents an increased plasticity, and the local cortical circuits can adapt to the visual stimuli received. After the end of the critical period, the circuits established in the visual cortex are resilient to reorganization, and plastic re-adaptation of the circuits is more difficult.

During the critical period, amblyopia can be treated due to the transiently plastic nature of the visual cortex resulting in an improvement of the visual acuity in the amblyopic eye and thus, amblyopia can be treated in children under the age of 5 prior to the end of the critical period. However, there are several factors that can prevent successful treatment. Firstly, in many cases where children present a mild form of amblyopia, the condition will remain undetected until tested further at older ages when it is too late for successful treatment. Secondly, some patients have problems with compliance to the treatment, which often requires a long treatment period. And thirdly, socioeconomic factors can limit treatment, as shown by a higher rate of amblyopia in less favorable environments [5]. As a result, amblyopes suffer from several visual functional abnormalities, includ-

ing reductions in visual acuity, contrast sensitivity function, spatial distortion, abnormal spatial interactions, and impaired contour detection. Amblyopia is difficult to treat in older patients past the critical period for ocular dominance plasticity because even when vision is restored to the occluded eye, mature cortical circuits are resistant to remodeling their connections. Primary visual cortex is only weakly driven by previously deprived inputs, and fails to recover high visual acuity after the occlusion is removed. Therefore, one possibility to treat this disease and restore high acuity vision in amblyopes is to reactivate the plastic state of visual cortex in a post-critical period state. In this regard, a required first step into the restoration of critical period plasticity in adults is to understand precisely why immature circuits are so malleable.

Computation of information in the cortex is achieved mainly by the interaction between excitatory and inhibitory neurons. The maturation of the inhibitory circuit is a critical event in the experience-dependent phase of visual system development. Neuronal response properties is in part mediated by neurotrophic signaling which is independently regulated in inhibitory neurons compared to their excitatory neuron counterparts, for instance the neurotrophic tyrosine kinase receptor ErbB4 is expressed exclusively in inhibitory neurons in the cortex [6]. While parvalbumin-positive (PV) neurons are identified as the major population of cortical inhibitory neurons [7], how PV neurons modulate circuitry and plasticity in visual cortex has begun to emerge only recently. Direct recording of the activity of genetically labeled PV neurons during visual deprivation using state-of-the-art multi-photon guided in-vivo recording in alert mice unexpectedly shows that PV neuron activity must decrease for ocular dominance plasticity to proceed. This rapid plasticity of inhibitory circuits during deprivation in the young leads to disinhibition of cortical activity and is permissive for subsequent plasticity among excitatory neurons [8]. These results indicate that strong local cortical inhibitory circuits produced by PV neurons might prevent plastic reorganization of visual cortex

in adults. However, an important question that remains unanswered is whether modulation of the activity of PV neurons in the visual cortex is sufficient to reactivate the plastic state.

We are aiming at answering this important question by using multiple techniques, such as intrinsic signal optical imaging of the visual cortex, multi-photon guided in-vivo recording of genetically labeled neurons, recording of neuronal activity by measuring intracellular calcium levels in-vivo, and controlling the activity of genetically identified neuronal subpopulations using optogenetic techniques. Our goal is to understand the mechanisms involved in the increased plasticity observed in visual cortical networks during the critical period, which would then allow us to develop strategies to transiently revert adult cortical plasticity levels to that present in young, critical period-aged circuits. The knowledge gained in studying these important questions about the development of cortical circuits would be of great importance in understanding and treating the disease, so that both visual responsiveness and high acuity can be gained in amblyopes that did not receive a proper treatment during visual critical period. Recently Dr. Diego Pafundo has received a $60,000 Career-Starter Research Grant from the Knights Templar Eye Foundation for this study. The Knights Templar Eye Foundation [9] seeks to improve vision through research, education and supporting access to care. The Career-Starter Research Grants fund scientists and physicians at the beginning of their academic careers who plan to conduct research on vision diseases that can be treated or prevented.

> "The Knights Templar Eye Foundation seeks to improve vision through research, eduation, and supporting access to care."

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